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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,521	02/15/2000	PETER E. NIELSEN	ISIS-3070	8096

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	28

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/424,521	Applicant(s) NIELSEN, PETER E.	
	Examiner J. Douglas Schultz	Art Unit 1635	

-- The MAILING DATE of this communicati n app ars on th cover she t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-27,31-34,38-41,45-48 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23-27,31-34,38-41,45-48 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Arguments

1. Applicants' response filed April 7, 2003 has been considered. Applicants' incorporation of material into the instant specification by reference from the parent U.S. Patent Number 5,539,082 has been fully entered. Rejections and/or objections not reiterated from the previous office action mailed January 15, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. In response to applicants' entry of essential material that was incorporated by reference to the parent U.S. Patent Number 5,539,082, it is noted that said entry is sufficient to overcome the rejection of record made under 35 U.S.C. § 112 1st paragraph written description, for incorporating new matter. The following rejection is a reinstatement of previous rejections as indicated below; applicants arguments filed December 19, 2002, which were directed to these rejections, are addressed below.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

4. Claims 23, 25-27 and 31 are rejected under 35 U.S.C. 102(a) as being anticipated by PCT Patent Application WO/92/20702 for the same reasons of record as set forth in the Office action

mailed April 3, 2002. Applicants' arguments filed December 19, 2002 have been fully considered but they are not persuasive.

Applicants argue that the rejection of claims 23, 25-27 and 31 made in the previous Office Action under 35 U.S.C. 102(a) over PCT Patent Application WO/92/20702 ("the 702 application") should be withdrawn, because Applicants assert that the 702 reference does not actually describe the claimed invention in a way that would place it in the possession of those skilled in the art, and that the examiner therefore must have engaged in picking and choosing from among many variables of the 702 application.

It is important to note at the outset that the '702 reference is related via continuations and continuations-in part to the instant application, but that priority is not presently claimed. For this reason, the 702 reference is considered for prior art.

The argument that the previous Office action engaged in picking and choosing in order to arrive at applicants claimed invention is not adopted, since the compounds of the 702 application are substantially identical to the presently claimed compound. Importantly, applicants' response effectively acknowledges this in the most previous amendment, by adding material to the instant specification from a priority document in order to overcome a new matter rejection; this matter, which also appears in the 702 reference, was previously argued by applicant to be improperly picked and chosen by the examiner in forming the instant rejection.

During the prosecution history of the instant application, applicants had previously argued that a particular preferred structure (structure III) of the '702 reference was not anticipatory because the 702 reference taught only the options of $C(O)CH_3$ or H at the important R_i/R_j position, and not the elements of alkyl, lipid, or steroid as instantly claimed. However, this

was not convincing, because the 702 reference also taught a structure generic to structure III that specifically named the elements of alkyl, lipid, or steroid at the position occupied by R_i/R_j in structure III. At that time, applicant argued that the generic structure of the 702 reference could not be considered anticipation, because to do so would require improper picking and choosing of the alkyl, lipid, or steroid elements at the R_i/R_j position. However, when the Office discovered that the reference to alkyl, lipid, or steroid were not mentioned in the instant applcation and were thus considered to be new matter, applicants response was to explicitly add this matter from U.S. Patent Number 5,539,082 (082), which is a parent that was incorporated by reference. The 702 reference and the 082 reference appear to be identical in disclosing both structure III, and its generic structure, and the same substituents, including alkyl, lipid, or steroid elements in the same manner. Applicants now argue that this incorporated material from the 082 patent provides support for the insertion of alkyl, lipid, or steroid elements at the R_i/R_j position, even though these elements are only referred to in the generic structure of the 082 patent. Thus, applicants are now relying upon essential material that was previously argued to be improperly picked and chosen.

Furthermore, the scope of all possible embodiments of structure III of the 702 application (pages 4-10) is substantially the same as the instantly claimed product. Structure III of the 702 application provides a generic structure of a peptide nucleic acid (PNA), which is also the subject of the present application. Structure III is identified as the preferred embodiment of such a PNA, shares identical core structure with and possesses all of the limitations of the presently claimed compounds and thus clearly anticipates said compounds. Specifically, both structure III of the 702 application and the instantly claimed compounds possess identically

placed carbon/nitrogen structures, along with R_h, L, R_7 and R_i groups (the instantly claimed compositions also comprises an R_j group that may become part of the R_i group). The R_h groups of both the instantly claimed compositions and of the structure III composition may only be OH, NH2, or NHlysNH2. The L-groups of both may be naturally occurring nucleobases. The R_7 groups of both may either be a hydrogen or an amino acid. Finally, the language of the instant claims allows for merging R_i and R_j into one group that is analogous to the R_i group of structure III of the 702 application, and both may be alkyl groups. Contrary to Applicants assertion, there are not many variables from which to choose from; in fact, the scope of variables is quite close between the reference and the instantly claimed composition. Thus, all elements of the presently claimed compounds are present, rendering the instantly claimed compounds and related methods as being clearly anticipated by the teachings of the 702 application.

Applicants have argued that structure III cannot anticipate the instant compound because the "k", "l", and "m" may be selected from 0-5, that there are 216 possibilities among these moieties alone, and imply that there is no guidance given as to which of these 216 is preferred. Insofar as applicants imply that there is no guidance among the 216 possibilities, this is plainly misleading. For example, the instant application requires that "k" be 0, and that "m" be 2, which of course equals 2. The 702 reference states that k+m is preferably 1 or 2. Thus applicants argument that one must select from amongst 216 possibilities glides over the reality that one is led directly to a very small number of embodiments that describe applicants claimed invention by the disclosure of the 702 reference itself.

Thus, the 702 reference, when taken in view of applicants amendment, teaches all the elements of the presently claimed compound. The compound of the 702 application contains

relatively few options for substitution, most of which match identically with the substitutions claimed in the instant application. Finally, because all elements of the compound are anticipated in the reference, and because the scope of compound of the 702 application is identical in most respects to the scope of the compound of the instant claims, there was no picking and choosing necessary to produce the instantly claimed product, thus rendering applicant's arguments unpersuasive.

Claims 21, 23-27, 31-34, and 38 rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teaching of the 702 application and Renneissen et al. (J. Biol. Chem, (1990), 265 pp.16337-16342), for the same reasons of record as set forth in the Office action mailed April 3, 2002.

Applicants argue that the reference of Renneissen does not cure the defects of the 702 reference, and as such this combination can't produce the claimed invention. Since the compound of the present invention is anticipated by the reference as discussed above, the rejection of obviousness as set forth in the previous office action was particularly directed to the combination of the instant compound *in liposomes*. However, as outlined above, the 702 refernece is not considered to carry deficits; since applicants have not pointed out any defects other than those discussed above, or provided any further arguments, the rejection of record is maintained.

Claims 39-41, 45-48, and 52 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record.

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that the specification discloses adequate support, including sites and modes of administration, dose level and administration regimens. Applicants allege that no evidence of record refuting applicants assertion that the claimed invention is enabled. Applicants also argue that therapeutic data is not needed to adequately teach that effect, and that some experimentation is allowed to determine optimum parameters of treatment.

These arguments are not adopted. It is first noted that despite repeated assertions that no evidence has been provided by the Office in supporting the instant enablement rejection, applicant is reminded that multiple cited references have been provided to applicant in support of the Office position. Although the Office bears the initial burden of setting forth a reasonable explanation of why applicants are not deserving of the scope claimed, the references and reasoning already provided are considered to constitute a prima facie case of enablement. Despite applicants insistence, the burden of persuasion has shifted to applicant to support the claim of enablement as a result.

As discussed in previous Office Actions, the present invention is complex, and therapeutic applications using compounds analogous to those claimed here are undeveloped. The reason they are undeveloped is that there remain several well-known but unsolved problems in the art that persist as obstacles to the practice of the invention as claimed. As previously outlined, and despite the prophetic treatment regimens provided in applicant's disclosure, the ability of the oligos to penetrate cells and reach their targets is largely unpredictable. These compounds are

poorly taken up by cells. Once inside the cell, the RNA targets typically have already assumed folded conformations that prevent oligo hybridization to the target, further decreasing the likelihood of predicting success. Further, the immune system response to foreign matter in general, and oligonucleotides and their derivatives in particular, can be dramatic and irregular, and can lead to a number of maladaptive responses. Finally, oligonucleotides and their derivatives can bind unpredictably to blood proteins and other elements, further complicating efforts to predict *a priori* whether a particular PNA treatment will ever work. Applicants' response is notably silent in addressing these issues that were raised in the previous Office action, and has provided no evidence to rebut the teachings outlined above.

Since these issues remain unresolved in the art, and since the prophetic guidance disclosed in the specification does not address how to overcome these obstacles, one of ordinary skill in the art would not be able to make and use the invention without undue experimentation with any predictable degree of success.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
June 29, 2003

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600